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Air pollution and female fertility: a systematic review of literature

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Abstract

Air pollution is a cause of concern for human health. For instance, it is associated with an increased risk for cancer, cardiovascular and respiratory disorders. In vitro and in vivo studies suggested that air pollutants could act as endocrine disruptors, promote oxidative stress and exert genotoxic effect. Whether air pollution affects female infertility is under debate. The aim of the present study was to conduct a systematic review of studies that evaluated the impact of air pollution on female infertility. We systematically searched the MEDLINE (PubMed) and SCOPUS databases to identify all relevant studies published before October 2017. No time or language restrictions were adopted, and queries were limited to human studies. We also hand-searched the reference lists of relevant studies to ensure we did not miss pertinent studies. The risk of bias and quality assessment of the studies identified were performed using the Newcastle-Ottawa Scale. Primary outcomes were conception rate after spontaneous intercourse and live birth rate after in vitro fertilization (IVF) procedures. Secondary outcomes were first trimester miscarriage, stillbirths, infertility, number of oocytes and embryo retrieved. Eleven articles were included in the analysis. We found that in the IVF population, nitrogen dioxide and ozone were associated with a reduced live birth rate while particulate matter of 10 mm was associated with increased miscarriage. Furthermore, in the general population, particulate matter of 2.5 mm and between 2.5 and 10 mm were associated with reduced fecundability, whereas sulfur dioxide, carbon monoxide and nitrogen dioxide might promote miscarriage and stillbirths. The main limitation of our findigns resides in the fact that the desegn of studies included are observational and retrospective. Furthermore, there was a wide heterogenity among studies. Although larger trials are required before drawing definitive conclusions, it seems that air pollution could represent a matter of concern for female infertility.

Keywords: Air pollution, IVF, Miscarriage, Live birth rate

Introduction

Female infertility has increased in recent years [1]. It was estimated that this condition affects 1 in seven couples in developed countries [2]. Most cases of female infertility are related to specific disorders, namely, ovulatory disorders, endometriosis, chromosomal abnormalities and male factors [3–7]. There is also evidence that air pollutant could play a role in the pathogenesis of female infertility [8–10]. Air pollution appears to be a cause of concern for human health. For instance, it has been associated with an increased risk of cancer [11], and cardiovascular [12] and respiratory disorders in adults and children [13, 14]. In addition, air pollutants have been associated with adverse perinatal outcomes [15, 16].

Anthropogenic activities, namely traffic, industrial facilities and combustion of fossil fuels, which are particularly intense in large cities and in proximity of farms, are the main sources of health-related air pollutants. Air pollutants are in four main categories: gaseous pollutants (sulfur dioxide [SO_2], nitrate oxide [NO_2] and carbon monoxide [CO]), organic compounds (organic solvents or dioxins), heavy metals (lead and copper) and particulate matter (PM_{10} $PM_{2.5\text{-}10}$and $PM_{2.5}$) [17]. Ingestion and inhalation are the most common routes of exposure [17]. Ingestion is also facilitated by the fact that air pollution contributes to the contamination of food and water [18]. Some air pollutants, namely Cu, Pb and diesel exhaust seem to

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exert endocrine activity [19] that could affect female reproduction. Moreover, these endocrine "disruptors" exert estrogenic, antiestrogenic and antiandrogenic activity and some could interfere with the thyroid axis and influence metabolic disorders, such as insulin resistance and obesity, which are strictly related to infertility [20–22]. The increase in female infertility seems to parallel the increase in toxic emissions, which suggests that the impact of air pollution on human health could increase in the next years [23, 24]. In an attempt to summarize current evidence, we carried out a systematic review of studies devoted to the impact of air pollutions on female infertility.

Material and methods

Protocol and eligibility criteria

The present study was exempt from institutional and ethics board approval because it did not involve human intervention. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. The selection criteria are described according to PICO (Patients, Intervention, Comparison, and Outcomes). In detail, we evaluated fertility outcomes in women on reproductive age (in the general and IVF populations) in relation to exposure to air pollutants (Additional file 1: Table S1).

Search strategy

We conducted a systematic search using MEDLINE (PubMed) and SCOPUS databases to identify all relevant studies published before October 2017. Combinations of the following keywords and MESH search terms were used: "air pollutants" AND ("miscarriage" OR "embryo" OR "pregnancy" OR "IVF OR "fecundability" OR "infertility" OR "menstrual disorders"). No time or language restrictions were adopted, and queries were limited to human studies. We also hand-searched reference lists of relevant studies to ensure we did not miss pertinent studies.

Selection of studies

Four reviewers (G.C., M.M., G.CO and P.D.) independently evaluated titles and abstracts. Duplications were removed using Endnote online software and manually. Disagreements were resolved by discussion with a third authors (A.C. and C.D.), and if required, with the involvement of the most experienced authors (R.P.,C.A., G.D.). Articles were included only if they appeared in peer-reviewed journals. Case series, case reports, book chapters, congress abstracts and grey literature [26], which includes a range of documents not controlled by commercial publishing organization, were not included.

Data extraction

Data were extracted independently by four reviewers (G.C., M.M., G.CO and P.D.) using predefined data fields, including study quality indicators. Discrepancies were resolved by discussion with the senior authors (R.P., C.A. and G.D.).

Risk of bias, summary measures and synthesis of the results

The risk of bias and quality assessment of the included studies were performed adopting the Newcastle-Ottawa Scale (NOS) [27]. Four authors (A.C, C.D., G.C. and P.D.) independently assessed the risk bias for each study. The senior authors (R.P., C.A. and G.D.) resolved conflicts. The NOS score was used to evaluate the studies included, and judgment on each one was passed according to three issues: selection of the study group, comparability between groups, and ascertainment of exposed/not exposed cohorts. Primary outcomes were conception rate after spontaneous intercourse and live birth rate after IVF procedures. Secondary outcomes were first trimester miscarriage, stillbirths, infertility, number of oocytes retrieved and embryos transferred.

Results

Study selection and characteristics

A total of 4687 items were identified (Pubmed 2834 and Scopus 1853). A total of 2013 duplicates were removed manually and using the EndNote online library. The titles and abstracts of 2674 papers were scrutinized and 21 full papers were assessed for eligibility. Ten papers were excluded because they did not fulfill the inclusion criteria. Eleven articles were included in the analysis (Fig. 1). The characteristics of the studies included in the present study are reported in Table 1.

Risk of bias

The risk of bias was evaluated with the NOS score and is reported in Table 1.

Summary of results

We summarized our findings considering per each pollutant both IVF women and reproductive age women in general population (Table 2).

NO_2

IVF cycles

Increases in NO_2 concentrations were significantly associated with a lower live birth rate especially from embryo transfer to pregnancy test (OR 0.76, 95% CI 0.66–0.86, per 0.01 ppm increase) [28]. No effect on the number of oocytes retrieved or embryo transferred was observed [28].

General population

In a cross-sectional study involving women of reproductive age between 15 and 40 years, the fertility rate was not

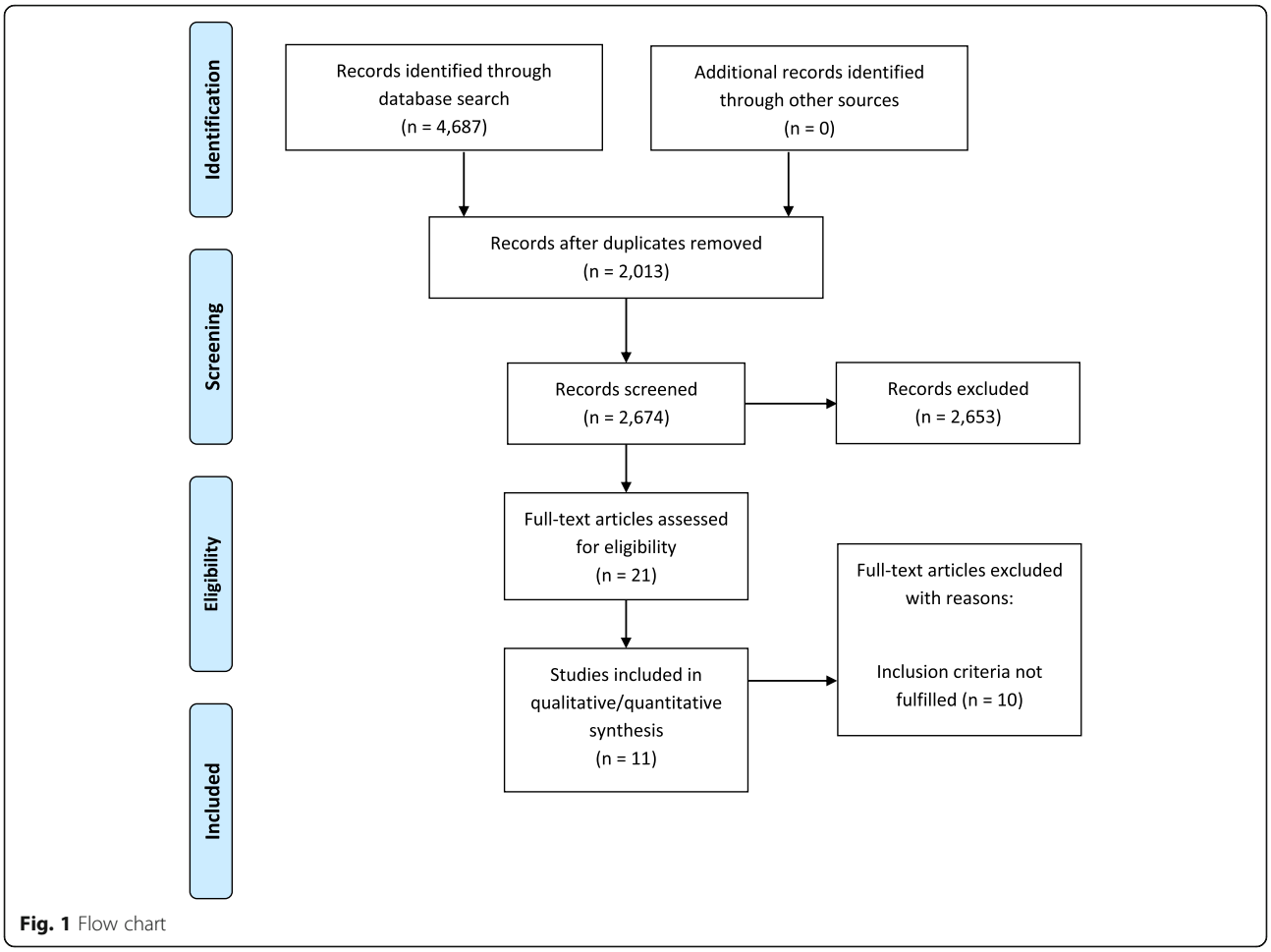

Fig. 1 Flow chart

significantly associated with NO_2 exposure (OR 0.97, 95% CI 0.94–1.003) [9]. In contrast, another retrospective cohort study, showed that there was a significant decreased fecundability ratio per each increase of 10 μg/m^3 NO_2 exposure (OR 0.72, 95% CI 0.53–0.97) [29]. Miscarriage rate was significantly increased in women exposed to NO_2 compared to not exposed group (OR 1.16, 95% CI 1.01–1.28, per each 10-ppb increase in NO_2 concentration) [30].

CO

General population

Exposure to CO was significantly associated with stillbirth in the second (OR = 1.14, 95% CI: 1.01, 1.28) and third trimester (OR = 1.14, 95% CI: 1.06, 1.24) [30]. No significant association with first trimester miscarriage was reported (OR = 1.14, 95% CI 0.98, 1.32) [30].

O_3

IVF-cycles

A detrimental effect was observed in terms of live birth rate in women exposed to O_3 from embryo transfer to date of live birth (OR 0.62, 95% CI 0.48–0.81, per 0.02 ppm increase) [28]. No effect on the number of oocytes retrieved or embryo transferred was observed [28].

General population

Only one study assessed the fecundability rate in the general population but no difference was reported between exposed and unexposed group [29].

$PM_{2.5}$

IVF cycles

Exposure to $PM_{2.5}$ during embryo culture was associated with a decreased conception rate (OR 0.90, 95% CI 0.82–0.99, per 8 μg/m^3 increase) but not with live birth rates [28]. No effect on the number of oocytes retrieved or embryo transferred was observed [28].

General population

Multivariate hazard ratio (HR) analysis did not reveal any association with infertility considering 2 years average exposure (HR 1.09, 95% CI 0.77–1.55), 4 years average exposure (HR 0.91, 95% CI 0.78–1.05) and cumulative average exposure (HR 1.05, 95% CI 0.93–1.20) [8]. Consistently, in another trial multivariate analysis did not reveal

Table 1 Characteristics, findings and risk of bias of included studies

Author, Year, (ref)	Study design	Population Country	Individuals	Pollutants	Exposure	Confounders adjusted for	Significant effect size:	Effect size	95% CI	NOS
Dejmek et al. (2000) [33]	Retrospective cohort	Czech Republic	2585 (General population)	SO2	Monitoring station obtained from by US EPA (Air Quality System)	Maternal age; parity; conception; seasonality; currently married; temperature average; temperature maxima; signal; year; season; epidemiological situation	Conception in the first unprotected menstrual cycle	OR = 0.57 SO2 levels (40-80 μg/m^3)	0.37–0.88	7
								OR = 0.49 SO2 levels (≥ 80 μg/m^3)	0.29–0.81	
Sallmen et al. (2008) [34]	Retrospective cohort	Portugal	406 (General population)	Solvents used in shoe manufacturing (N-hexane and hexane isomers; Toluene; Methyl ethyl ketone; Acetone; Ethyl acetate; dichloromethane)	Air sampling was performed in the personal breathing zones of the exposed women, spanning roughly an 8-h work shift.	Female age; Last method of contraception; Age at menarch; Regularity of menstrual cycle; Male smoking; Female and male use of alcohol; Male exposure to metal dusts or fumes; Male exposure to engine exhausts.	Fecundability density ratio (low exposure to solvents)	FDR = 0.55	0.40–0.74	7
							Fecundability density ratio (high exposure to solvents)	FDR = 0.70	0.52–0.94	
Green et al. (2009) [35]	Prospective cohort	USA	4979 (General population)	Traffic pollutants: NO2; O3; PM 2.5; PM 10, CO2 CH4, CO, H2S, NMHC NMOC; SO2; sulphur; THC	Traffic exposure were constructed using annual average daily traffic (AADT) counts near each residence and distance from residence to major roads	Maternal age, race, employment status, stressful life events and maternal smoking	Spontaneous abortion Maximum daily traffic within 50 m^2			7
							> 90 centile	OR = 1.18	0.87–1.60	
							> 90 centile (African American)	OR = 3.11	1.26–7.66	
							> 90 centile (non smokers)	OR = 1.47	1.07–2.04	
Mohorovic et al. (2010) [36]	Prospective cohort	Croatia	260 (General population)	Coal combustion (NO2; CO2; CO; other products)	Monitoring station (Labin meteorological station)	Crude data	Spontaneous abortion	OR = 2.99	0.91–9.80	5
Perin et al. (2010) [31]	Retrospective cohort	Brazil	348 (IVF women)	PM10	PM10 concentrations taken from 14 monitoring stations categorized into quartiles (Q1-Q4).	Ovarian response patterns to gonadotrophins, exposure, patient's age, and the year of IVF treatment	Miscarriage in IVF women (> 56.72 μg/m3)	OR = 5.05	1.04–25.51	8
							Live birth rates (> 56.72 μg/m3)	OR = 1.71	0.72–4.09	
Perin et al. (2010) [32]	Retrospective cohort	Brazil	177 (IVF women) 354 (General population)	PM10	PM10 concentrations taken from 14 monitoring stations categorized into quartiles (Q1-Q4).	Ovarian response patterns to gonadotrophins, exposure, patient's age, and the year of IVF treatment	Miscarriage in general population (> 56.72 μg/m3)	OR = 2.72	1.51–4.89	7
							Miscarriage in IVF women (> 56.72 μg/m3)	OR = 2.32	1.00–5.43	
Legro et al. (2010) [28]	Retrospective cohort	USA	7403 (IVF women)	PM2.5 PM10 SO2 NO2 O3	Monitoring station obtained from by US EPA (Air Quality System)	Age, IVF center and the year and season of oocyte retrieval	Live Birth Rate NO2 (after embryo transfer) O3 (after embryo transfer):	OR = 0.76 OR = 0.62	0.66–0.86 0.48–0.81	9

Table 1 Characteristics, findings and risk of bias of included studies *(Continued)*

Author, Year, (ref)	Study design	Population Country Individuals		Pollutants	Exposure	Confounders adjusted for	Significant effect size:	Effect size	95% CI	NOS
							Pregnancy rate PM2.5 (during embryo culture)	OR = 0.94	0.82–0.99	
Faiz e al. (2012) [30]	Retrospective cohort	USA	343,077 (General population)	PM 2.5 SO2 NO2 CO	Central monitoring station monitored by Agency Air Quality System	Maternal age; Race/Ethnicity; Educational level; Prenatal care; Smoking; Neighborhood socioeconomic status; Calendar year; month of conception and; mean temperature	Stillbirths NO2 (first trimester) SO2 (first trimester) CO (second trimester)	 OR = 1.16 OR = 1.13 OR = 1.14	 1.03–1.31 1.01–1.28 1.06–1.24	8
Slama et al. [29]	Retrospective cohort	Czech Republic	1916 (General population)	SO2, PM2.5, NO2, O3, carcinogenic PAHs	Central monitoring station	Maternal age, smoke habits and alcohol consumption before pregnancy,maternal education, marital status, BMI	Fertility rate PM2.5 NO2	FR = 0.78 FR = 0.72	0.65–0.94 0.53–0.97	9
Nieuwenhuijsen et al. (2014) [9]	Cross-sectional	Spain	not available (General population)	PM10 PM2.5 PMcoarse fraction NO2 NOx O3 PM2.5 adsorbance	Land use regression developed in the European Study of Cohorts for Air Pollution Effects	Socioeconomic status, ethnicity, age, educational level	Fertility rate PM coarse fraction	FR = 0.88	0.83–0.94	7
Mahalingaiah et al. (2016) [8]	Prospective cohort	USA	36,294 (General population)	PM 10, PM 2.5, PM 2.5–10	USEPA Air Quality System	Age, smoking status, Race, BMI, parity, rotation shift work, oral contraception use, diet, Census tract level median income and median home value	Hazard ratio of primary and secondary infertility Living closer a major roads	HR = 1.11	1.02–1.20	9

Table 2 Synthesis of results

Type of Pollutant	Population	Effect
NO_2	IVF	Lower live birth rates
	General population	Higher miscarriage rate
CO	General population	Higher stillbirth in second and third trimester
O_3	IVF	Lower live birth rates
$PM_{2.5}$	IVF	Lower pregnancy rates
	General population	Reduced fecundability ratio
PM_{10}	IVF	Higher miscarriage rate
	General population	Higher miscarriage rate
$PM_{2.5–10}$	General population	Reduced fertility rate
SO_2	IVF	No effect
	General population	Higher early miscarriage and third trimester still births. Reduced conception rate
Traffic pollutants	General population	Higher miscarriage rate; Higher infertility rates.
Coal combustion products	General population	Higher trend of miscarriage

any association with fertility rate [9]. On the other hand, The adjusted fecundability ratio was significantly decreased with each increase of 10 units (0.78, 95% CI 0.65–0.94) [29]. No statistically significant difference was observed in terms of late (second and third trimester) or early miscarriage (first trimester) [30].

$PM_{2.5–10}$

General population

Multivariate HR analysis did not reveal any association between infertility and $PM_{2.5–10}$ considering 2-year average exposure (HR 1.10, 95% CI 0.98–1.23), 4 year average exposure (HR 1.05, 95% CI 0.93–1.19) and cumulative exposure (HR 1.10, 95% CI 0.99–1.22) [8]. Conversely, another study reported a significant reduction of spontaneous fertility rate in women exposed to $PM_{2.5–10}$ (incidence risk ratio: 0.88, 95% CI 0.84, 0.94) [9].

PM_{10}

IVF cycles

No significant effect was observed in terms of live birth rate, number of oocytes retrieved or embryos transferred in exposed women undergoing their first IVF cycle [28]. Furthermore, no significant effect was observed in the amount of gonadotropin used, number of oocytes retrieved, number of MII oocytes, embryo quality, clinical and live birth rate [26, 31]. A higher risk of miscarriage was observed in women with a higher exposure to PM_{10} (> 56.72 μg/m^3) comparing with those exposed to lower amount of PM_{10} (≤ 56.72 μg/m^3) (OR 5.05 95% CI 1.04–25-51) [31].

General population

Multivariate adjusted HR analysis per year did not reveal any association with infertility considering 2 years average exposure (HR 1.04, 95% CI 0.96–1.11), 4 years average exposure (HR 0.99, 95% CI 0.91–1.08) and cumulative average exposure (HR 1.06, 95% CI 0.99–1.13) infertility [8]. Multivariate incidence risk (IRR) ratio adjusted did not reveal any association between PM_{10} exposure and fertility rate (IRR 0.99, 95% CI 0.96–1.02) [9]. A significant association with early miscarriage was observed in women exposed to over 56.72 μg/m3. [32].

SO_2

IVF cycles

Exposure to SO_2 did not significantly affect birth rate, number of oocytes retrieved or embryos transferred in women undergoing their first IVF cycle [28].

General population

No differences in terms of adjusted fecundability rate was observed per an increase of 10 units in the SO_2 pollutant levels [29]. Conversely, in another study, the fecundability in the first unprotected menstrual cycle was significantly reduced only in couples exposed in the second month before conception to the following SO2 levels: 40–80 μg/m^3 (OR 0.57, 95% CI 0.37–0.88); ≥ 80 μg/m^3 (OR 0.49, 95% CI 0.29–0.81) [33]. The adjusted odds of miscarriage were significantly associated to SO_2 exposure (OR 1.13, 95% CI 1.01–1.28 per each 3 ppb increase in concentration) [30].

Organic solvents

General population

Female exposure to air contaminated with organic solvents (hexane and hexane isomers, toluene, methyl ethyl ketone, acetone, ethyl acetate, isopropyl alcohol and dichloromethane, n-hexane, hexane isomers and toluene) was associated with reduced fecundability density ratio (FDR = 0.55, 95% CI 0.40–0.74) for low exposure (exposure index 0.01–0.14), and for high exposure (exposure index > 0.14), (FDR = 0.70, 95% CI 0.52.0.94). Moreover, exposure for less than 6 years was more strongly associated with reduced FDR in both low (FDR = 0.50, 95% Cl 0.30 to 0.83) and high exposure groups (FDR = 0.50, 95% CI 0.28–0.90) [34].

Traffic pollutants

General population

In a large cohort study involving 4979 women, traffic pollutants were associated with an increased but not with significant risk of miscarriage rate among women exposed to a maximum annual average of traffic pollutants within

50 m (AOR 1.18 95%, CI 0.87–1.60). A significant association was observed in a subgroup analysis involving African Americans (AOR = 3.11; 95% CI, 1.26–7.66) and nonsmokers (AOR = 1.47; 95% CI, 1.07–2.04) [35]. In another large cohort study, women living closer to a major road had a higher risk of infertility than did women living far from a major road (HR, 1.11 95% CI: 1.02–1.20) [8].

Coal combustion pollutants

General population

In a small prospective study of 260 women, the miscarriage rate was higher, albeit not significantly, in women exposed to coal combustion pollutants than in non-exposed women (OR 2.99, 95% CI 0.91–9.80) [36] .

Discussion

Only 11 studies have evaluated the potential effect of air pollutants on female reproduction.. In the IVF context, NO_2 and O_3 were associated with impaired live-birth rates. In addition, exposure to high levels of PM_{10} (> 56.72 μg/m^3) resulted in an increased miscarriage rate after IVF procedures. Consistently, no study reported a significant effect on other quantitative (i.e. number of oocytes retrieved, number of embryos transferred, and consumption of gonadotropin) and qualitative (embryo quality, and number of MII oocytes) IVF outcomes [28, 31, 32]. In natural conception, reduced fecundability was associated with solvents and SO_2 [33, 34]. Notably while abortion rate was associated with traffic pollutants [8, 35], and in particular SO_2 and NO_2 [30], no clear relation to coal combustion pollutants emerged [36]. Contrasting findings between infertility and $PM_{2.5–10}$ were reported [8, 9].

Only three retrospective studies evaluated the effects of air pollution on IVF [28, 31, 32]. Although Legro and colleagues studied a large IVF population, the heterogeneity of IVF protocols and the lack of information about male partners represent two important limitation factors [28]. Moreover, the two studies conducted by Perin et al., are limited by the fact that only one pollutant was investigated and by the low number of cases enrolled [31, 32].

Eight studies have been conducted on the general population. Of the three prospective studies, the one by Mahalingaiah et al. is the largest (more than 36,000 patients) and has the highest qualitative NOS score [8]. The quality of evidence was lowest in the study by Mohorovic et al. as was the number of observations, and the authors did not report effect size for each air pollutant separately [36]. The same weakness emerges in the Green et al. paper, which however analyzed such important factors as work exposure, residential history and employment status of the population studied [35]. Of the five retrospective studies conducted to-date, the quality of evidence is highest in two large studies conducted by Faiz and colleagues [30] and by Slama and colleagues [29] demonstrating that air pollutants significantly affect fertility and stillbirths rates. The remaining three retrospective studies have several limitations, namely a paucity of data regarding the population studied [9], a low number of pollutant analyzed [33] and the methods adopted to assess exposure [34].

The relationship between air pollutants and spontaneous fertility was first observed in an animal model [37]. In detail, Mohallem et al. observed an increased implantation failure rate and a significant reduction of births in mice exposed to polluted city air compared to non-exposed mice [38]. Similarly, Veras et al. found significantly fewer antral follicles and a lower fertility index in mice exposed to traffic pollutants versus non-exposed mice [39].

The effect of air pollutants on human spermatogenesis has also been investigated [40–43]. The largest study, conducted by Hammoud et al., reported that $PM_{2.5}$ exposure negatively correlated with sperm morphology and motility [40]. The negative effect of particulate matter was confirmed in a recent prospective cohort study that identified a significant association between PM_{10} and $PM_{2.5}$ and sperm chromosomal abnormalities (i.e. disomy Y and disomy chromosome 21) [44].

The mechanism underlying the effect of air pollutants on female fertility is still a matter of debate. Several pathogenetic mechanisms have been proposed. Firstly, it was hypothesized that air pollutants could mimic the effect of androgens and estrogens in humans [45]. These endocrine-disrupting properties could exert their effect by interacting with nuclear receptor, the estrogen or androgen repertory or by interacting with specific targets in cytosol thus resulting in activation of the /Ras/Erk pathway [46]. Others have suggested that air pollutants could promote oxidative stress and inflammatory processes [17]. In this sense, we recently demonstrated that the addition of anti-oxidant factors to ovarian stimulation could improve reproductive outcome in women with polycystic ovarian syndrome [47]. However, whether antioxidant products could mitigate the effect of air pollutants on IVF outcomes remains to be determined. Finally, it has been suggested that air pollutants could exert a genotoxic effect. For instance, increased sperm DNA fragmentation was associated with exposure to elevated air pollution levels (at or above the upper limit of US air quality standards) [48]. Furthermore, DNA methylation seems to be significantly influenced by air pollutants [49]. Indeed, in a recent study of 777 men, an increase in air pollutant concentrations was significantly associated with F3, ICAM-1, and TLR-2 hypomethylation, and IFN-γ and IL-6 hypermethylation [50].

Our review has several limitations. First, most of the studies included in our analysis are observational and retrospective, and hence more prone to bias. Second, exposure ascertainment was heterogeneous among studies.

Most of the trials assessed air quality using a specific air monitoring station, others estimated exposure according to proximity to the potential source [8, 35, 36]. In addition, the reference levels of each pollutant varied significantly among studies. Lastly, the populations investigated as well as the definitions used to assess infertility and miscarriage were also heterogeneous. These factors render a meta-analytic and quantitative approach to this issue challenging.

In conclusion, our meta-analysis suggests there is a close association between female infertility and air pollution. However, a more robust meta-analytic approach is required before any definitive conclusion can be reached.

Additional file

Additional file 1: Table S1. Selection criteria according to PICO questions. (DOCX 14 kb)

Abbreviations

AOR: Adjusted Odds ratio; BMI: Body mass index; CO: Carbon monoxide; Cu: Copper; ERK: Extracellular Signal-regulated Kinase; F3: Tissue factor; FDR: Fecundability density ratio; HR: Hazard ratio; ICAM-1: Intercellular adhesion molecule 1; IL-6: Interleukin-6; INF-γ: Interferon gamma; IRR: incidence risk ratio; NO_2: Nitrogen dioxide; NMHC: Non-Methane hydrocarbons; NMOC: Non-Methane organic compounds; NOS: Newcastle-Ottawa Scale; O_3: Ozone; OR: Odds ratio; Pb: Lead; PM_{10}: Particulate matter of 10 μm; $PM_{2.5}$: Particulate matter of 2.5 μm; $PM_{2.5–10}$: Particulate matter of 2.5–10 μm (coarse fraction).; RAS: Signal transducing protein; SO_2: Sulphur dioxide; SRC: Signal transducing protein tyrosine kinase; THC: Total hydrocarbons; TLR-2: Toll-like receptor 2

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CA, RP, GP and AC conceived the study. AC drafted the first version. MM, GC, CD, GC and PD contributed to data search and quality assessment. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable (review of published papers).

Consent for publication

Not applicable (review of published papers).

Competing interests

The authors declare that they have no competing interests.

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